PHARMACOLOGIC THERAPY OF POSTMENOPAUSAL OSTEOPOROSIS: AN UPDATED NARRATIVE REVIEW OF GUIDELINES AND EVIDENCE

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ABSTRACT

Postmenopausal osteoporosis is a highly prevalent skeletal disorder that confers a substantial burden of fragility fractures, disability, loss of independence, and mortality. Over the past two decades, several potent antiresorptive and osteoanabolic agents have transformed clinical care. Yet, real-world treatment gaps persist and the optimal choice, sequencing, and duration of therapy remain the subject of evolving guidance. This narrative review synthesizes contemporary international and national guideline recommendations, pivotal randomized trials, and extension studies bearing on the pharmacologic management of postmenopausal osteoporosis. We discuss oral and parenteral bisphosphonates, denosumab, teriparatide and abaloparatide, romosozumab, selective estrogen receptor modulators (SERMs), menopausal hormone therapy, and calcitonin, with emphasis on efficacy against vertebral, nonvertebral, and hip fractures; time to benefit; adverse effects including atypical femoral fractures and osteonecrosis of the jaw; drug holidays; and the increasingly important concepts of sequential and goal-directed therapy. We also highlight updated guideline algorithms for risk stratification, the role of FRAX and recency of fracture, and pragmatic strategies for monitoring response and minimizing rebound phenomena after treatment discontinuation. Evidence supports a tailored approach that aligns drug choice and sequence with absolute fracture risk and patient comorbidity, prioritizing antiresorptives for most high-risk patients and an anabolic-first strategy for the very-high-risk phenotype.

INTRODUCTION

Worldwide, osteoporotic fractures represent a major cause of morbidity, with hip and vertebral fractures carrying the greatest clinical impact. Contemporary guidance from endocrine and bone societies converge on the need to identify high- and very-high-risk women and initiate effective therapy promptly after a fragility fracture, ideally within weeks, to reduce imminent risk. The 2024 UK National Osteoporosis Guideline Group (NOGG) update and recent papers from the International Osteoporosis Foundation (IOF) underscore persistent undertreatment and advocate system-level solutions alongside optimized pharmacotherapy. FRAX® remains central for absolute fracture risk estimation, now calibrated to >80 countries and with adjustments for fracture recency available in FRAXplus®. In clinical practice, treatment thresholds and the choice of first-line therapy depend on age, bone mineral density (BMD), fracture history and recency, glucocorticoid exposure, and comorbidity including cardiovascular disease. [1–6, 16–20, 43].

Risk Stratification and When to Treat

Current guidelines categorize risk on the basis T-scores, prior fractures, FRAX probabilities, and markers of imminent risk. Women with a recent vertebral or hip fracture, multiple fractures, very low T-scores (e.g., ≤ -3.0), or high glucocorticoid exposure fall into very-high-risk categories wherein anabolic-first strategies or potent parenteral antiresorptives are preferred. Those at high risk without the very-high-risk features often begin with an oral bisphosphonate or yearly intravenous zoledronic acid. FRAX 10-year probabilities guide initiation in women without prior fractures, and country-specific intervention thresholds are recommended. The updated NOGG guidance provides a clear algorithm mapping clinical probabilities to initial therapy and emphasizes early post-fracture intervention within fracture liaison services. [1–5, 16–20].

Overview of Pharmacologic Classes

The principal pharmacologic classes include bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), the RANKL inhibitor denosumab, osteoanabolic agents teriparatide and abaloparatide (PTH analogs) and romosozumab (sclerostin inhibitor with dual anabolic/antiresorptive effects), SERMs (raloxifene and bazedoxifene), menopausal hormone therapy (MHT), and calcitonin with limited contemporary indications. The selection among these agents balances antifracture efficacy at key sites, tolerance and adherence profiles, renal function, injection preferences, concomitant disease, and safety considerations such as cardiovascular risk for romosozumab and rebound risk following denosumab cessation. [1–6, 8–15, 21–44].

Figure 1. Pragmatic Treatment Algorithm (Flowchart)

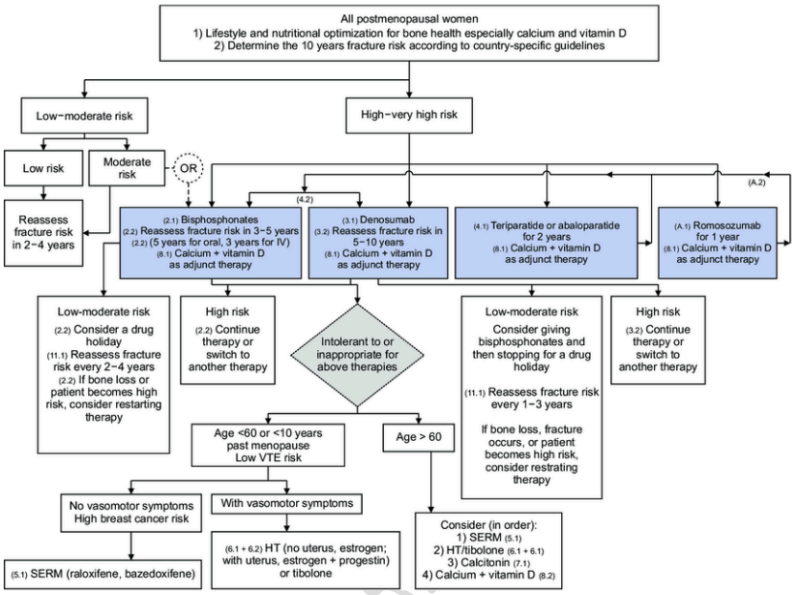


Figure one algorithm outlines a risk-stratified approach to postmenopausal osteoporosis management. It emphasizes early identification of fracture risk severity to guide personalized therapy—favoring anabolic-first strategies for very-high-risk patients and antiresorptives for others—while integrating lifestyle measures, supplementation, and vigilant reassessment to optimize long-term skeletal outcomes and prevent fracture recurrence.[1–7, 8–12, 22–25, 29–33, 37–44,49]

Bisphosphonates

Bisphosphonates remain the bedrock of antiresorptive therapy. Alendronate and risedronate reduce vertebral, nonvertebral, and hip fractures in randomized trials, with risedronate demonstrating reduced hip fractures in elderly women with osteoporosis in the HIP trial. Ibandronate robustly reduces vertebral fractures but evidence for hip fracture reduction is limited, making it a spine-predominant agent. Once-yearly zoledronic acid in the HORIZON Pivotal Fracture Trial reduced vertebral, hip, and nonvertebral fractures and produced durable BMD gains. Practical considerations include upper gastrointestinal intolerance for oral agents, adherence challenges with strict dosing instructions, and post-infusion flu-like reactions with zoledronic acid. Rare but important adverse events associated with long-term exposure include atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ), though their absolute risks are low and outweighed by prevented osteoporotic fractures over 3–5 years of therapy. Duration of therapy and the possibility of a “drug holiday” after 3–5 years for moderate-risk patients are informed by FLEX (alendronate) and HORIZON

(zoledronic acid) extension data, as well as ASBMR task force guidance. [7–10, 22–28, 34–41]. Table 1 describes selected efficacy and characteristics of Bisphosphonates

Table 1. Selected Efficacy and Characteristics of Bisphosphonates

Agent	Regimen	Vertebral fracture reduction	Nonvertebral/hip evidence	Key trials and notes
Alendronate	70 mg weekly oral	Significant	Nonvertebral and hip reduction demonstrated	FIT and FLEX; durable benefit; consider holiday after 5 years in moderate risk [24–26, 28]
Risedronate	35 mg weekly oral	Significant	Hip reduction in osteoporotic elderly women	HIP trial; benefit greatest with low BMD at baseline [24, 27, 29]
Ibandronate	150 mg monthly oral or 3-monthly IV	Significant vertebral reduction	Limited evidence for hip reduction	BONE study; consider spine-predominant risk [24, 30]
Zoledronic acid	5 mg IV yearly	Significant	Significant hip and nonvertebral reduction	HORIZON PFT and extensions; acute-phase reactions manageable [11, 27]

Denosumab

Denosumab, a monoclonal antibody to RANKL, produces potent suppression of bone resorption and increases in BMD with half-yearly subcutaneous dosing. In the pivotal FREEDOM trial, denosumab significantly reduced vertebral, nonvertebral, and hip fractures, with sustained efficacy and safety through 10 years in extension studies. Denosumab is attractive in patients with renal impairment where bisphosphonates are limited, and in those intolerant of oral therapy. The central caveat is the rebound phenomenon upon discontinuation—rapid rise in bone turnover markers, loss of BMD gains within months, and increased risk of multiple vertebral fractures—necessitating planned sequential antiresorptive therapy, typically with zoledronic acid or a potent oral bisphosphonate, timed to the next due dose. Recent reviews refine risk factors and mitigation strategies, though complete prevention of rebound fractures is not guaranteed. Counselling must emphasize adherence to 6-monthly dosing and a structured exit plan. [11–14, 29–33].

Figure 2. Denosumab Discontinuation: Consolidation Strategy (Flowchart)

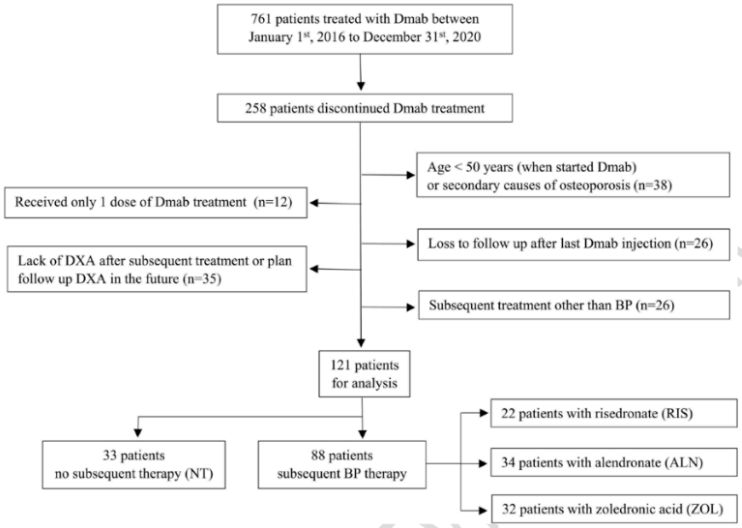


Figure 2illustrates the clinical pathway following denosumab discontinuation, emphasizing transition to bisphosphonate therapy—particularly intravenous zoledronic acid—to prevent rebound bone loss. It highlights individualized timing based on bone turnover and density monitoring, ensuring ongoing fracture surveillance and optimal skeletal protection after cessation of denosumab therapy.

[29–33],[50]

Osteoanabolic Therapies: Teriparatide and Abaloparatide

Teriparatide (PTH 1–34) and abaloparatide (PTHrPanalog) stimulate bone formation, rapidly increase spine BMD, and reduce vertebral fractures; teriparatide also reduces clinical nonvertebral fractures in high-risk women. The head-to-head VERO trial showed teriparatide superiority over risedronate for vertebral and clinical fractures in women with severe osteoporosis. Abaloparatide in ACTIVE significantly reduced vertebral and nonvertebral fractures compared with placebo, with a lower rate of hypercalcemia than teriparatide, and the ACTIVExtend sequence demonstrated sustained fracture reduction when followed by alendronate. The approved duration of PTH analog therapy is limited (generally up to 24 months lifetime exposure for teriparatide and 18 months for abaloparatide), after which transition to a potent antiresorptive is essential to preserve gains. Anabolic-first sequencing, particularly for very-high-risk phenotypes with recent vertebral fractures or very low T-scores, achieves larger and faster BMD gains and superior early fracture risk reduction than antiresorptive-first strategies. [18, 21, 35–39]. Table 2 shows osteoanabolic agents along with theirefficacy and use.

Table 2. Osteoanabolic Agents: Efficacy and Use

Agent	Duration	Vertebral	Nonvertebral	Hip	Typical next step
Teriparatide, 20 μg SC daily	Up to 24 mo	Strong reduction	Reduction in clinical fractures; mixed for hip	Limited direct hip data	Follow with zoledronic acid or denosumab
Abaloparatide, 80 μg SC daily	18 mo	Strong reduction	Reduction observed	Limited direct hip data	Follow with alendronate or IV bisphosphonate; ACTIVExtend support

[20, 23, 37–41].

Romosozumab

Romosozumab inhibits sclerostin, producing a dual effect of stimulating bone formation and decreasing resorption. In FRAME and especially ARCH (romosozumab for 12 months followed by alendronate versus alendronate alone), substantial early gains in BMD and greater reductions in vertebral and clinical fractures were observed in women at high fracture risk. Regulatory labeling carries a boxed warning regarding potential increased risk of myocardial infarction, stroke, and cardiovascular death, based primarily on imbalances in the ARCH trial year-1 comparisons to alendronate. Contemporary guidance recommends avoiding initiation in women with MI or stroke in the prior year and caution in those with high cardiovascular risk. After the 12-month romosozumab course, transition to an antiresorptive is required to maintain gains. Ongoing analyses continue to evaluate the cardiovascular signal, but label precautions remain in place. [6, 7, 12, 40–42]. Table 3 summarises key points on Romosozumab.

Table 3. Romosozumab: Key Points

Feature	Evidence summary
Rapid BMD gains at spine and hip within 6–12 months	Consistent across trials; larger than antiresorptives over the same period [6, 12]
Greater reduction in vertebral and clinical fractures versus alendronate over 24 months in ARCH	Supports anabolic-first in very-high-risk patients [6, 12]
CV boxed warning	Avoid initiation within 1 year of MI/stroke; weigh risks in high CV risk [40–42]
Mandatory follow-on antiresorptive	Maintains BMD and antifracture benefits [6]

SERMs and Menopausal Hormone Therapy

Raloxifene and bazedoxifene reduce vertebral fractures and can be considered in younger postmenopausal women with spine-predominant risk and low absolute hip risk, especially where breast cancer risk reduction is desirable. They do not convincingly reduce hip fractures and increase the risk of venous thromboembolism. MHT reduces fractures in the Women's Health Initiative but is limited by risks that outweigh benefits for primary fracture prevention in older women. It may be considered in recently menopausal, symptomatic women at low cardiovascular and breast cancer risk where fracture risk reduction is an ancillary benefit rather than the primary indication. [30–33, 44–48].Table 4 describes various SERMs and MHT in Postmenopausal Osteoporosis.

Table 4. SERMs and MHT in Postmenopausal Osteoporosis

Class	Fracture efficacy	Typical candidate
Raloxifene	Vertebral reduction; no proven hip reduction	Postmenopausal women with spine-predominant risk and desire for breast cancer risk reduction; avoid if high VTE risk [44–47]
Bazedoxifene	Vertebral reduction; possible nonvertebral benefit in higher-risk subgroups	Similar to raloxifene; international availability varies [46–47]
MHT	Reduces fractures; risk-benefit unfavorable in older women	Symptomatic, recently menopausal, low CV/breast cancer risk; osteoporosis prevention as secondary objective [48]

Calcitonin

Intranasal salmon calcitonin formerly held an indication for postmenopausal osteoporosis with vertebral pain, but concerns about modest efficacy and potential cancer risk signals have led to restricted use in many regions. It is not a first-line therapy in contemporary guidelines and, where available, is mainly reserved for short-term analgesia after acute vertebral fracture rather than long-term antifracture therapy. [1–3].

Safety Considerations: AFF and ONJ

AFFs and ONJ represent rare but serious complications occurring predominantly with long-term antiresorptive use. The absolute AFF risk remains very low relative to the number of typical osteoporotic fractures prevented by bisphosphonates, particularly within the first 3–5 years of therapy. ONJ risk is higher with oncology-dose antiresorptives than with osteoporosis doses; in the latter setting it remains uncommon, although dental risk factors, poor oral hygiene, denture use, invasive dental procedures, and prolonged exposure increase risk. Shared decision-making should include these risks, but the benefit-to-risk balance strongly favors treatment in appropriately selected patients. Drug holidays with bisphosphonates may mitigate cumulative AFF risk; in contrast, drug holidays are contraindicated with denosumab due to rebound vertebral fracture risk. [34–41].

Duration, Drug Holidays, and Monitoring

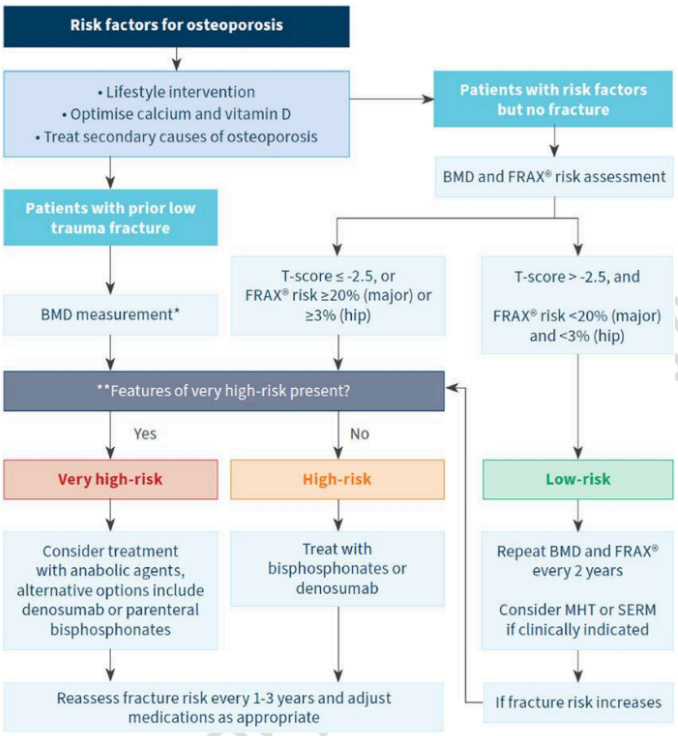
Guidelines recommend periodic reassessment after 3–5 years of oral bisphosphonates or 3 years of IV zoledronic acid to determine whether to continue therapy or institute a holiday in

moderate-risk patients. Continuation is favored in those with very low hip BMD, prior vertebral or hip fracture, or fractures on therapy, given evidence from FLEX and HORIZON extensions that continuation reduces morphometric vertebral fractures and better maintains BMD. During a drug holiday, patients should undergo clinical surveillance, BMD monitoring approximately every 2–3 years, and earlier re-initiation if fractures occur, BMD declines substantially, or risk escalates. For denosumab, there is no safe holiday; stopping requires timely administration of a potent bisphosphonate with monitoring of bone turnover markers to ensure adequate suppression. [22–27, 29–33].

Sequential and Goal-Directed Therapy

Emerging guidance endorses "goal-directed" management, aligning therapy choices and sequences to reach explicit treatment targets (e.g., femoral neck T-score thresholds) and minimize time spent at very high risk. An anabolic-first strategy with romosozumab or a PTH analog followed by a potent antiresorptive is particularly compelling for women with recent vertebral fractures, multiple fractures, or profoundly low BMD, as early, large BMD gains correlate with greater fracture risk reduction. Conversely, most high-risk patients without very-high-risk features can begin with a bisphosphonate or denosumab and transition according to response and tolerability. The choice between denosumab-based and bisphosphonate-based sequences should consider renal function, adherence, dental risk, and the necessity to plan for denosumab consolidation therapy to avoid rebound. [5, 6, 12, 19]. Figure 3 summarises Sequential Therapy while treating postmenopausal osteoporosis.

Figure 3. "Sequential Therapy Playbook" (Schematic)



Interpretation:

This schematic outlines phenotype-driven sequencing in postmenopausal osteoporosis therapy, aligning initial treatment intensity with fracture risk. It emphasizes individualized transition between anabolic and antiresorptive agents, renal and cardiovascular safety considerations, and the "lock-in" principle ensuring sustained skeletal protection after anabolic or denosumab discontinuation.[51]

Practical Considerations: Implementation and Adherence

Fragility fracture pathways and fracture liaison services improve treatment initiation and persistence. Achieving calcium and vitamin D adequacy, educating about correct oral bisphosphonate administration, scheduling on-time denosumab injections, and arranging timely transition after finite anabolic or romosozumab courses are essential operational steps. NOGG 2024 emphasizes streamlined assessment, early parenteral therapy post-fracture, and systematic follow-up. Utilization of FRAXplus® adjustments for fracture recency or multiple prior fractures can refine risk estimation and increase the appropriateness of anabolic-first strategies where warranted. [1–3, 16–20].

Figure 4. Site-Tailored Therapeutic Alignment in Postmenopausal Osteoporosis

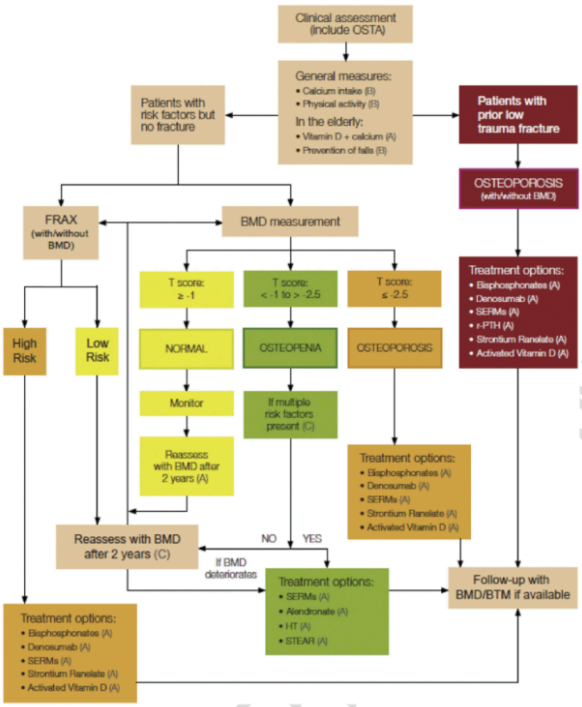


Figure 4 illustrates treatment individualization based on skeletal site predominance of fracture risk. It emphasizes aligning pharmacologic choice with spine versus hip vulnerability, integrating anabolic and antiresorptive strategies to optimize both vertebral and nonvertebral protection while ensuring consolidation therapy to preserve bone mass and reduce recurrent fracture risk. [6, 9, 12, 18, 21]

Monitoring Response and When to Switch

Clinical endpoints include incident fractures and changes in BMD by DXA at 1.5–2-year intervals. Lack of expected BMD gain or new fractures on therapy prompts evaluation of adherence, secondary causes (e.g., hyperparathyroidism, malabsorption), and, in some cases, intensification or a mechanistic switch (from antiresorptive to anabolic or vice versa). Bone turnover markers can aid in assessing bisphosphonate adherence or denosumab rebound but should complement, not replace, clinical outcomes and BMD. A goal-directed approach encourages switching if targets are not met within reasonable intervals. [5, 19].

Conclusion

Pharmacologic therapy for postmenopausal osteoporosis is highly effective when matched to risk and delivered in sequences that preserve structural gains. For most high-risk women, bisphosphonates or denosumab remain appropriate initial options with strong vertebral,

nonvertebral, and hip fracture efficacy. In women at very high risk—especially those with recent vertebral fractures, multiple fractures, or very low T-scores—an anabolic-first strategy with romosozumab or a PTH analog followed by a potent antiresorptive maximizes early risk reduction and long-term durability. Denosumab requires planned consolidation to avoid rebound vertebral fractures upon discontinuation; bisphosphonates permit risk-stratified drug holidays. The 2024 NOGG guidance and contemporary positions from endocrine and bone societies, along with FRAXplus® refinements, support a pragmatic, goal-directed approach that integrates site-specific efficacy, patient preferences, comorbidity, and systems that close the persistent treatment gap. [1–7, 9–12, 15–19, 21–48].

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